REMARKS

Claims 29, 30 and 33-41 have been canceled.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Election of Species

The Examiner states that the claims will be examined only to the extent that they read on *in vivo* method of modulating neural cells with Sonic hedgehog protein and on anoxia-induced ischemia. Applicants understood the election of anoxia-induced ischemia to be for search purposes only, such that the full scope of disorders encompassed by the claims would be examined upon finding that the anoxia-induced ischemia disorder is allowable. Clarification is requested.

Rejection of Claims 1-3, 23, 25, 26, 29 and 36-41 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-3, 23, 25, 26, 29 and 36-41 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner states that use of the term "hedgehog polypeptide" without reference to specific amino acid sequences are indefinite because the specification "does not identify that material element or combination of elements which is unique to, and therefore, definitive of 'hedgehog polypeptide[s]'."

Applicants respectfully disagree with the Examiner's characterization of the teachings of the specification and accordingly traverse the rejection. The specification teaches both structural and functional features of hedgehog polypeptides, such that a skilled artisan could determine the scope of the claims. For example, the passages at page 2, line 29 through page 3, line 26 and page 17, line 13 through page 19, line 27 disclose several hedgehog sequences and teach that hedgehog homologs can be identified through hybridization to the cDNA for the disclosed hedgehog polypeptides. In addition, hedgehog polypeptides "have apparent broad involvement in the formation and maintenance of ordered spatial arrangements of differentiated tissues in vertebrates, both adult and embryonic, and can be used to generate and/or maintain an array of different vertebrate tissue both in vitro and in vivo." Thus, based on the functional and structural

information provided in the specification, one skilled in the art could determine the scope of the term "hedgehog polypeptide." Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claim 25 Under 35 U.S.C. § 112, Second Paragraph

Claim 25 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner apparently objects to the recitation of "bioactive" and alleges that the specification has not established what are inductive events mediated by wild-type hedgehog proteins.

The Examiner's reading of the claim terminology is, at best, strained. The Examiner appears to wish that the specification explicitly list which type of induction events are mediated by wild-type hedgehog proteins. There is no reason for the specification to have such disclosure, because, as described in the Background of the Invention, induction events were well known as of the effective filing date of the application. With this knowledge, a skilled artisan could, for example, contact a tissue with a test polypeptide and a wild-type hedgehog protein and determine whether the test polypeptide causes an induction event similar to that of the wild-type hedgehog protein. Such an induction event would indicate that the test polypeptide is a bioactive polypeptide within the meaning of the present invention.

In addition, the specification provides ample description of a "bioactive" hedgehog polypeptide, such that a skilled artisan could readily ascertain the scope of the claim. Further description of inductive events can be found at page 16, lines 29-35 and page 21, lines 29-33.

Based on the knowledge a skilled artisan would have had as of the effective filing date and based on the teachings of the specification, a skilled artisan would readily be able to determine the scope of the term "bioactive." Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-3, 5, 6, 11-13, 23-26 and 42-56 Under 35 U.S.C. § 112, First Paragraph

Claims 1-3, 5, 6, 11-13, 23-26 and 42-56 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to meet the enablement requirement. The Examiner states that while the specification is enabling for methods of promoting growth, differentiation and/or

survival of embryonic neural cells by administering a sonic hedgehog polypeptide of SEQ ID NOS: 8, 11, 12 or 13 or an N-terminal autoproteolytic portion thereof, it does not enable use of a polypeptide other than one of SEQ ID NOS: 8, 11, 12 or 13 or other than N-terminal autoproteolytic portions thereof. The Examiner further states that the specification is not enabling for promoting growth, differentiation and/or survival of neuronal cells other than embryonic cells. The Examiner then makes several assertions as alleged support for these reasons, which Applicants address below in the order in which they appear in the Office Action.

First, the Examiner asserts that specification discloses that neuronal cells grown *in culture* readily lose their differentiated state. Given that only *in vivo* methods are presently being examined, it is not understood how this is relevant to the patentability of the instant claims. Moreover, the Examiner's reading of the specification is highly selective and misleading. The specification simply states that loss of differentiation is commonly observed when neuronal cells are grown in culture from adult tissue and when such cells form a blastema during regeneration. Importantly, the specification includes means for ensuring an adequately restrictive environment to maintain neuronal cells at various states of differentiation (page 59, lines 18-21). There is no indication that loss of differentiation is a concern *in vivo*, such as in the claimed methods.

Second, the Examiner asserts that one of ordinary skill in the art would expect that adult tissues would not be responsive to sonic hedgehog polypeptides in the same way that embryonic tissues are or would even be unresponsive, because experiments indicate that sonic hedgehog protein is not expressed in adult tissues. Applicants traverse this aspect of the rejection on three grounds. Applicants disagree with the reasoning behind the Examiner's assertion. In addition, the Examiner has used an improper basis to determine whether the instant claims are enabled. Furthermore, as discussed below, post-filing evidence clearly shows that this assertion is incorrect and, under the correct enablement standard, that the specification sufficiently enables the claims.

Expression of hedgehog, or any extracellular signaling protein, in a tissue is not required for that tissue to be sensitive to signaling activated by that extracellular signaling molecule. It is the expression on particular cells of the receptor for that signaling molecule that is required for the tissue to be sensitive. In the case of hedgehog signaling, one of skill in the art would expect that cells which can be influenced by treatment with a hedgehog polypeptide generally express the receptor patched. Applicants note that the application provides no evidence regarding

expression of a hedgehog receptor that would guide one of skill in the art away from practicing the methods disclosed in the application.

Applicants additionally point out that medical science is rife with treatments that involve administering protein and non-protein drugs, which are not endogenously expressed, in order to achieve a beneficial effect. Certainly humans don't endogenously express aspirin, and yet this compound is taken daily by millions of people to treat a range of conditions. Furthermore, specific hormones are now typically prescribed to replace hormones whose levels are either reduced with age or lost due to disease or surgical intervention. Estrogen replacement therapy is used, not only for menopausal women whose estrogen levels are declining, but also for women who have undergone ovarectomy or radical hysterectomy. Such women no longer endogenously express estrogen, yet the persistence of estrogen receptors allows their bodies to respond to exogenously supplied estrogen. Similarly, some men who undergo surgical castration to treat testicular cancer are given exogenous testosterone. These examples indicate that one of skill in the art would not construe the mere absence of expression of a particular protein as evidence that the protein would not have an effect on that tissue. To the contrary, the lack of expression of a protein suggests that expression of the protein is regulated because the protein would continue to have an effect on a cell.

The test for enablement is not whether one of skill in the art believes that the invention will work as Applicants have described. A patent application is neither a peer reviewed publication nor a grant proposal, and Applicants need not seek the approval of any or all of the research community in order to have an operable and enabled invention. Rather, the standard for enablement is whether one of skill in the art can practice the invention in light of Applicants' disclosure. Applicants submit that one of skill in the art could practice the claimed invention following the teachings of the disclosure even if he or she did not believe that Applicants' invention would work. Accordingly, Applicants contend that the claims are enabled throughout their scope, and that post-filing evidence (discussed below) further supporting the claimed subject matter does not demonstrate that undue experimentation is required to practice the claimed methods. Rather, such post-filing evidence merely confirms the teachings of the disclosure.

Applicants are citing post-filing evidence which demonstrates that, as taught by the application as filed, sonic hedgehog polypeptides can be used to influence the proliferation,

differentiation and survival of adult cells including neuronal cells. Applicants contend that the wealth of post-filing evidence supports the enablement of the claimed subject matter. Simply put, Applicants taught that hedgehog polypeptides can be used to influence the behavior of adult cells including neuronal cells, and hedgehog polypeptides can in fact be used to influence the behavior of adult cells including neuronal cells.

Applicants are providing a copy of the declaration of Hank Dudek (Exhibit 1), originally submitted in parent Application No. 08/854,771, which demonstrates that Sonic hedgehog influences the fate of neuronal cells in animals following nerve crush. This evidence is one of many examples that exist and demonstrate that hedgehog polypeptides influence both neuronal and non-neuronal adult cell fate. By way of example, Applicants provide herewith a few Exhibits that demonstrate that hedgehog polypeptides influence the proliferation, differentiation, and/or survival of adult endothelial cells, pancreatic cells, and taste buds (Pola et al., 2001; Thomas et al., 2000; Miura et al., 2001; enclosed herewith as Exhibits 2-4). Additionally, Applicants enclose herewith a copy of a declaration under 35 U.S.C. 1.132 of Lee Rubin that was submitted in parent Application No. 08/905,572 (Exhibit 5). The declaration of Lee Rubin provides evidence that both Sonic hedgehog and Indian hedgehog affect the growth and proliferation of adult cartilage explants, and furthermore that systemic administration of Sonic hedgehog induces chondrocyte proliferation in vivo. Exhibits 1-5 provide just a few non-limiting examples that illustrate the effectiveness of hedgehog polypeptides in a range of adult tissues.

Applicants also direct the Examiner's attention to the large number of examples which demonstrate that hedgehog polypeptides influence neuronal cell proliferation, differentiation, and/or survival ("Focus on ALS", 2000; Tsuboi and Shults, enclosed herewith as Exhibits 6-7). Briefly, "Focus on ALS" is an article summarizing work presented at the Fifth Annual Diabetic Neuropathy Meeting which included a study demonstrating an improvement in both sensory and motor nerve function in diabetic mice treated for five weeks with Sonic hedgehog protein (Exhibit 6). Tsuboi and Shults provide evidence demonstrating that intrastriatal injection of Sonic hedgehog reduces behavioral deficits in rats with an injury to the nigrostriatal system caused by administration of 6-OHDA (Tsuboi and Shults, 2002, Exhibit 7). The efficacy of hedgehog polypeptides in animals treated with 6-OHDA is particularly interesting since lesions caused by 6-OHDA are considered to provide a model for Parkinson's disease.

In addition to these published studies, Applicants direct the Examiner's attention to data provided in a number of applications licensed or assigned to Applicants. Example 1 of United States Serial Number 09/187,387 demonstrates that administration of Sonic hedgehog reduces the deficits produced by cisplatin-induced neuropathy. Example 1 of United States Serial Number 09/418,221 demonstrates that Sonic hedgehog decreases the volume of cerebral infarct in a rat stroke model produced by occluding the middle cerebral artery. Examples 2-6 of United States Serial Number 09/325,602 demonstrate the efficacy of Sonic hedgehog in rats with a 6-OHDA induced lesions. As outlined above, such lesions are believed to provide an in vivo model of Parkinson's disease. Finally, Example 7 of United States Serial Number 09/325,602 demonstrates the efficacy of Sonic hedgehog treatment in rats following malonate-induced striatal lesions. These lesions are viewed as an in vivo model for Huntington's disease.

The Examiner also asserts that the specification provides no guidance regarding the nature of the response of adult tissues to sonic hedgehog. This is simply incorrect. The specification clearly contemplates treatment of disorders in adult tissues. See, for example, page 63, lines 12-31, which provides a listing of disorders that are expected to be treatable using hedgehog polypeptides. Thus, there is no basis for the Examiner's further assertion that one of skill in the art would be required to perform undue experimentation to determine which of the multitude of adult neural cells is responsive to sonic hedgehog. In addition, Applicants refer to the post-filing evidence discussed above to demonstrate that a skilled artisan could have performed the claimed methods in accordance with the specification and without undue experimentation.

The Examiner has cited a few references, which state that the role of hedgehog signalling is poorly documented and that "there is no direct correlation between the neuron phenotypes induced by Shh [Sonic hedgehog] and those supported by Shh in a trophic manner." However, the evidence presented above outweighs the value of these references. These references, at best, show that the effects of Sonic hedgehog are limited in certain cellular models. In contrast, the evidence described above show that Sonic hedgehog is effective in the claimed methods in a wide variety of circumstances.

The Examiner also states that "the claims encompass an almost limitless number of polypeptides that comprise a portion of SEQ ID NO: 8, 11, 12, or 13" and that "[o]ne of skill in the art is left to extensive experimentation" to determine which amino acids can be varied.

Applicants point out that substantial evidence exists to demonstrate that the hedgehog signaling pathway is not as sensitive to sequence variation in the hedgehog protein as the Examiner's comments suggest. Chang et al. demonstrated that mouse Sonic hedgehog can functionally substitute for either Drosophila hedgehog or quail Sonic hedgehog (Chang et al., 1994, enclosed herewith as Exhibit 8). Furthermore, much of the data cited above to demonstrate that hedgehog polypeptides can influence adult cell fate were performed using a hedgehog polypeptide derived from a species other than the species in which the functional experiment was performed. For example, the experiments provided by Pola et al. use human Sonic hedgehog protein for in vivo experiments performed in mice, and the experiments performed by Tsuboi and Shults use human Sonic hedgehog protein for in vivo experiments performed in rats. The ability of hedgehog proteins derived from one species to function in another species demonstrates that hedgehog signaling is tolerant to some variation in the sequence of the hedgehog protein.

In addition, the specification presents multiple active sequences, which a skilled artisan could use as a starting point. The homologous regions in these sequences inherently provide guidance about the "sensitive regions" of the sequence. The homologous regions can be readily determined from Figures 2 and 4-6. In addition, the specification at page 44, line 26 through page 46, line 31 provides further guidance on developing additional active polypeptides.

In summary, Applicants contend that the evidence in the field overwhelmingly supports methods of influencing the proliferation, differentiation, and survival of cells using hedgehog polypeptides. In accordance with MPEP 2164.05, when making a determination as to the enablement provided for the claimed invention, the evidence must be considered as a whole. Furthermore, "the evidence provided by the applicant need not be conclusive but merely convincing to one skilled in the art." (MPEP 2164.05). Applicants contend that this burden has been satisfied.

Furthermore, Applicants point out that even if the claims encompass certain inoperative embodiments, that does not undermine the enablement of the operative subject matter. In accordance with MPEP 2164.08(b), "[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art." This standard has been upheld in the courts, and permits a claim to encompass a finite number of

inoperable embodiments so long as inoperable embodiments can be determined using methodology specified in the application without undue experimentation. See, for instance, *In re Angstadt*, 190 U.S.P.Q. 214 (CCPA 1976). Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 29, 30 and 33-41 Under 35 U.S.C. § 112, First Paragraph

Claims 29, 30 and 33-41 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. In order to expedite prosecution, Applicants have canceled these claims. Applicants reserve the right to pursue this subject matter in a continuing application. Withdrawal of the rejection is respectfully requested.

Rejection of Claims 1-3, 5, 6, 11-13, 23-26, 29, 30 and 33-56 Under 35 U.S.C. § 112, First Paragraph

Claims 1-3, 5, 6, 11-13, 23-26, 29, 30 and 33-56 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner states that there is no description of methods of promoting growth, differentiation or survival of adult neural cells. The Examiner further states that the description regarding hedgehog protein's effects on embryonic chicken tissues does not support the claimed genera of methods that would not be expected to behave the same way and that there appears to be no specific description of the claimed treatment regimes.

Applicants respectfully disagree with the Examiner's characterizations. First, one of ordinary skill in the art would expect the claimed methods to have the recited effects on promoting growth, differentiation or survival of adult neural cells based upon the teachings of the specification. As discussed in detail above, the specification explicitly contemplates the treatment of adult neural cells. See, for example, page 63, lines 12-31. Moreover, it is not understood how what a skill artisan "expects" pertains to the written description requirement. The written description requirement is concerned primarily with whether an applicant had possession of the invention at the time of filing. Applicants note that an invention need not be reduced to practice in order to fulfill the written description requirement. Second, it is not understood how specific description of the claimed treatment regimes relates to the written description requirement. The invention only needs to be adequately described to fulfill the

written description requirement. The Examiner has provided no reasons why the specification does not adequately describe how to perform the invention, particularly in view of the extensive post-filing evidence discussed above.

Applicants note that the Examiner has summarized case law regarding structural inventions. Applicants submit that such case law is not relevant to the present rejection, because the Examiner has not applied this case law to any structural elements (e.g., chemical structures, biopolymer structures) in the present invention.

Thus, the instant claims comply with the written description requirement. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945, under Order No. HMSU-P17-006.**

Respectfully Submitted,

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